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(54) Title: BENZAMIDES AND RELATED INHIBITORS OF FACTOR XA

(57) Abstract: Novel benzamide compounds including their pharmaceutically acceptable isomers, salts,hydrates, solvates and prodrug derivatives having activity against mammalian factor Xa aredescribed. Compositions containing such compounds are also described. The compounds andcompositions are useful *in vitro* or *in vivo* for preventing or treating coagulation disorders.

BENZAMIDES AND RELATED INHIBITORS OF FACTOR Xa

Field of the Invention

This invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa or when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation (e.g. thrombin, fVIIa, fIXa) or the fibrinolytic cascades (e.g. plasminogen activators, plasmin). In another aspect, the present invention relates to novel monoamidino-containing compounds, their pharmaceutically acceptable salts, and pharmaceutically acceptable compositions thereof which are useful as potent and specific inhibitors of blood coagulation in mammals. In yet another aspect, the invention relates to methods for using these inhibitors as therapeutic agents for disease states in mammals characterized by coagulation disorders.

Background of the Invention

Hemostasis, the control of bleeding, occurs by surgical means, or by the physiological properties of vasoconstriction and coagulation. This invention is particularly concerned with blood coagulation and ways in which it assists in maintaining the integrity of mammalian circulation after injury, inflammation, disease, congenital defect, dysfunction or other disruption. Although platelets and blood coagulation are both involved in thrombus formation, certain components of the coagulation cascade are primarily responsible for the amplification or acceleration of the processes involved in platelet aggregation and fibrin deposition.

Thrombin is a key enzyme in the coagulation cascade as well as in hemostasis. Thrombin plays a central role in thrombosis through its ability to catalyze the conversion of fibrinogen into fibrin and through its potent platelet activation activity. Direct or indirect inhibition of thrombin activity has been the focus of a variety of recent anticoagulant strategies as reviewed by Claeson, G., "Synthetic Peptides and Peptidomimetics as Substrates and Inhibitors of Thrombin and Other Proteases in the Blood Coagulation System", Blood Coag. Fibrinol. 5, 411-436 (1994). Several classes of anticoagulants currently used in the clinic directly or indirectly affect

thrombin (i.e. heparins, low-molecular weight heparins, heparin-like compounds and coumarins).

A prothrombinase complex, including Factor Xa (a serine protease, the activated form of its Factor X precursor and a member of the calcium ion binding, gamma carboxyglutamyl (Gla)-containing, vitamin K dependent, blood coagulation glycoprotein family), converts the zymogen prothrombin into the active procoagulant thrombin. Unlike thrombin, which acts on a variety of protein substrates as well as at a specific receptor, factor Xa appears to have a single physiologic substrate, namely prothrombin. Since one molecule of factor Xa may be able to generate up to 138 molecules of thrombin (Elodi et al., *Thromb. Res.* 15, 617-619 (1979)), direct inhibition of factor Xa as a way of indirectly inhibiting the formation of thrombin may be an efficient anticoagulant strategy. Therefore, it has been suggested that compounds which selectively inhibit factor Xa may be useful as *in vitro* diagnostic agents, or for therapeutic administration in certain thrombotic disorders, see *e.g.*, WO 94/13693.

Polypeptides derived from hematophagous organisms have been reported which are highly potent and specific inhibitors of factor Xa. United States Patent 4,588,587 describes anticoagulant activity in the saliva of the Mexican leech, *Haementeria officinalis*. A principal component of this saliva was shown to be the polypeptide factor Xa inhibitor, antistasin (ATS), by Nutt, E. *et al.*, "The Amino Acid Sequence of Antistasin, a Potent Inhibitor of Factor Xa Reveals a Repeated Internal Structure", J. Biol. Chem., 263, 10162-10167 (1988). Another potent and highly specific inhibitor of Factor Xa, called tick anticoagulant peptide (TAP), has been isolated from the whole body extract of the soft tick *Ornithidoros moubata*, as reported by Waxman, L., *et al.*, "Tick Anticoagulant Peptide (TAP) is a Novel Inhibitor of Blood Coagulation Factor Xa" Science, 248, 593-596 (1990).

Factor Xa inhibitory compounds which are not large polypeptide-type inhibitors have also been reported including: Tidwell, R.R. *et al.*, "Strategies for Anticoagulation With Synthetic Protease Inhibitors. Xa Inhibitors Versus Thrombin Inhibitors", Thromb. Res., 19, 339-349 (1980); Turner, A.D. *et al.*, "p-Amidino Esters as Irreversible Inhibitors of Factor IXa and Xa and Thrombin", Biochemistry, 25,

4929-4935 (1986); Hitomi, Y. *et al.*, "Inhibitory Effect of New Synthetic Protease Inhibitor (FUT-175) on the Coagulation System", Haemostasis, 15, 164-168 (1985); Sturzebecher, J. *et al.*, "Synthetic Inhibitors of Bovine Factor Xa and Thrombin. Comparison of Their Anticoagulant Efficiency", Thromb. Res., 54, 245-252 (1989); Kam, C.M. *et al.*, "Mechanism Based Isocoumarin Inhibitors for Trypsin and Blood Coagulation Serine Proteases: New Anticoagulants", Biochemistry, 27, 2547-2557 (1988); Hauptmann, J. *et al.*, *"Comparison* of the Anticoagulant and Antithrombotic Effects of Synthetic Thrombin and Factor Xa Inhibitors", Thromb. Haemost., 63, 220-223 (1990); and the like.

Others have reported Factor Xa inhibitors which are small molecule organic compounds, such as nitrogen containing heterocyclic compounds which have amidino substituent groups, wherein two functional groups of the compounds can bind to Factor Xa at two of its active sites. For example, WO 98/28269 describes pyrazole compounds having a terminal C(=NH)-NH_2 group; WO 97/21437 describes benzimidazole compounds substituted by a basic radical which are connected to a naththyl group via a straight or branched chain alkylene,-C(=O) or -$S(=O)_2$ bridging group; WO 99/10316 describes compounds having a 4-phenyl-N-alkylamidino-piperidine and 4-phenoxy-N-alkylamidino-piperidine group connected to a 3-amidinophenyl group via a carboxamidealkyleneamino bridge; and EP 798295 describes compounds having a 4-phenoxy-N-alkylamidino-piperidine group connected to an amidinonaphthyl group via a substituted or unsubstituted sulfonamide or carboxamide bridging group.

There exists a need for effective therapeutic agents for the regulation of hemostasis, and for the prevention and treatment of thrombus formation and other pathological processes in the vasculature induced by thrombin such as restenosis and inflammation. In particular, there continues to be a need for compounds which selectively inhibit factor Xa or its precursors. Compounds that have different combinations of bridging groups and functional groups than compounds previously discovered are needed, particularly compounds which selectively or preferentially bind to Factor Xa. Compounds with a higher degree of binding to Factor Xa than to

thrombin are desired, especially those compounds having good bioavailability and/or solubility.

Summary of the Invention

As discussed above, a number of non-peptide, specific, factor Xa inhibitors have been described either in the scientific or patent literature (Zhu and Scarborough, Ann. Rep. Med. Chem. 35: 83-102 (2000)). Most of these compounds rely on the interaction of P1 and P4 elements of the inhibitor compounds with the S1 and S4 sub-sites on the factor Xa enzyme. In general, it has been described that P1 elements utilize a highly charged benzamidine functionality in order to interact with the S1 pocket of the factor Xa enzyme. Furthermore, substitution on the benzamidine nitrogens either by alkylation or cyclization (cyclic amidines) of these previously described inhibitors is detrimental to their interaction with the enzyme at the S1 pocket. In the present application, a novel series of inhibitors of factor Xa which do not utilize a S1-interacting benzamidine but utilize a neutral P1 species are described. In addition the compounds also utilize a substituted benzamidine or a cyclic amidine as a P4 element which can each interact with the S4 sub-site of factor Xa enzyme. Surprisingly, the inhibitors of this invention with modified amidine elements are not only of high potency *in vitro*, but also have excellent pharmacological and pharmaceutical properties *in vivo*. These are results that would not have been predicted for such structures.

Accordingly, the present invention relates to novel compounds which inhibit factor Xa, their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives, and pharmaceutically acceptable compositions thereof which have particular biological properties and are useful as potent and specific inhibitors of blood coagulation in mammals. In another aspect, the invention relates to methods of using these inhibitors as diagnostic reagents or as therapeutic agents for disease states in mammals characterized by undesired thrombosis or which have coagulation disorders, such as in the treatment or prevention of any thrombotically mediated acute coronary or cerebrovascular syndrome, any thrombotic syndrome occurring in the venous system, any coagulopathy, and any thrombotic complications associated with

extracorporeal circulation or instrumentation, and for the inhibition of coagulation in biological samples.

In certain embodiments, this invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation cascade (e.g. thrombin, etc.) or the fibrinolytic cascade, and are useful as diagnostic reagents as well as antithrombotic agents.

In one embodiment, the present invention relates to a compound according to the formula (I):

A-Q-D-E-G-J-X (I)

where:

A is selected from:

(a) C_1-C_6-alkyl;

(b) C_3-C_8-cycloalkyl;

(c) -$N(R^1,R^2)$, $N(R^1,R^2)$-$C(=NR^3)$-, $N(R^1,R^2)$-$C(=NR^3)$-$N(R^4)$-, R^1-$C(=NR^3)$-, R^1-$C(=NR^3)$-$N(R^4)$-;

(d) phenyl, which is independently substituted with 0-2 R substitutuents;

(e) naphthyl, which is independently substituted with 0-2 R substitutuents; and

(f) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R substitutuents;

R is selected from:

H, halo, -CN, $-CO_2R^1$, $-C(=O)-N(R^1, R^2)$, $-(CH_2)_m-CO_2R^1$, $-(CH_2)_m-C(=O)-N(R^1, R^2)$, $-NO_2$, $-SO_2N(R^1, R^2)$, $-SO_2R^1$, $-(CH_2)_mNR^1R^2$, $-(CH_2)_m-C(=NR^3)-R^1$, $-(CH_2)_m-C(=NR^3)-N(R^1,R^2)$, $-(CH_2)_m-N(R^4)-C(=NR^3)-N(R^1,R^2)$, $-(CH_2)_mNR^1-$ group appended to a 3 to 6 membered heterocyclic ring containing from 1-4 heteroatoms selected from N, O and S, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, $-CF_3$, $-OR^2$, and a 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic system may be independently replaced with a member selected from the group consisting of halo, $-C_1-C_4$-alkyl, $-C_{1-4}$alkyl-CN, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl and $-NO_2$;

m is an integer of 0-2;

R^1, R^2, R^3 and R^4 are independently selected from the group consisting of:
H, $-OR^5$, $-N(-R^5, -R^6)$, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, $-C_{0-4}$alkylphenyl and $-C_{0-4}$alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, -CN, and $-NO_2$; or

R^1 and R^2, or R^2 and R^3 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl and $-NO_2$;

R^5 and R^6 are independently selected from the group consisting of:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and -NO_2; or

R^5 and R^6 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, -C_1-C_4-alkyl, -CN -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

Q is a member selected from the group consisting of:

a direct link, -CH_2-, -C(=O)-, -O-, -N(R^7)-, -N(R^7)CH_2-, - CH_2N(R^7) -, -C(=NR^7)-, -C(=O)-N(R^7)-, -N(R^7)-C(=O)-, -S-, -SO-, -SO_2-, -SO_2-N(R^7)- and -N(R^7)-SO_2-;

R^7 is selected from:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and -NO_2;

D is a direct link or is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0-2 R^{1a} substitutuents;

(b) naphthyl, which is independently substituted with 0-2 R^{1a} substitutuents; and

(c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be subsituted from 0-2 R^{1a} substitutuents;

R^{1a} is selected from:

halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, -NO_2, -$(CH_2)_nNR^{2a}R^{3a}$, -$(CH_2)_nCO_2R^{2a}$, -$(CH_2)_nCONR^{2a}R^{3a}$, -$SO_2NR^{2a}R^{3a}$, -SO_2R^{2a}, -CF_3, -OR^{2a}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN and -NO_2;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN and -NO_2;

n is an integer of 0-2;

E is a direct link or a member selected from the group consisting of:

-C_{1-2}-alkyl-, -O-, -S-, -SO-, -SO_2-, -C_{0-1}-alkyl-C(=O), -C_{0-1}-alkyl-C(=O)-N(-R^8)- C_{0-1}-alkyl-, -C_{0-1}-alkyl-N(-R^8)-C(=O)-C_{0-1}-alkyl-, -N(-R^8)-C(=O)-N(-R^8)- and -C_{0-1}-alkyl-N(-R^8)-;

R^8 is a member selected from the group consisting of:

H; -C_{1-4}-alkyl; -C_{0-4}-alkylaryl; -C_{0-4}-alkyl-heteroaryl; -C_{1-4}-alkyl-C(=O)-OH, -C_{1-4}-alkyl-C(=O)-O-C_{1-4}-alkyl, and -C_{1-4}-alkyl-C(=O)-N(-R^{2b}, -R^{3b});

R^{2b} and R^{3b} are each a member independently selected from the group consisting of:

H, -C_{1-4}-alkyl, -C_{0-4}-alkyl-aryl; -C_{0-4}-alkyl-heterocyclic group, and R^{2b} and R^{3b} together with the N atom to which they are attached can form a 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0-2 R^{1c} groups;

R^{1c} is a member selected from the group consisting of:

Halo; -C_{1-4}-alkyl; -CN, -NO_2; -C(=O)-N(-R^{2c}, -R^{3c}); -C(=O)-OR^{2c}; -$(CH_2)_q$-N(-R^{2c}, -R^{3c}); -SO_2-N(-R^{2c}, -R^{3c}); -SO_2R^{2c}; -CF_3 and -$(CH_2)_q$-OR^{2c};

R^{2c} and R^{3c} are each independently a member selected from the group consisting of:

H; -C_{1-4}-alkyl and -C_{1-4}-alkyl-aryl;

q is an integer of 0-2;

G is a member selected from the group consisting of:

(a) C_2-alkenyl or C_{3-8}-cycloalkenyl, wherein the alkenyl and cycloalkenyl attachment points are the alkenyl carbon atoms and wherein the -C_2-alkenyl or -C_{3-8}-cycloalkenyl are substituted with 0-4 R^{1d} groups;

(b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0-4 R^{1d} groups;

(c) a 3-8 membered a saturated, partially unsaturated or aromatic monocyclic- heterocyclic ring system containing 1-4 heteroatoms

selected from N, O and S, wherein 0-2 ring atoms of the heterocyclic ring may be substituted with 0-4 R^{1d} groups; and,

(d) an 8-10 membered fused heterocyclic bicyclic ring system, containing 1-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms of the fused bicyclic ring system may be substituted with 0-4 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

H, halo; C_{1-6}-alkyl, carbocylic aryl, -CN; $-NO_2$; $-(CH_2)_{0-6}-NR^{2d}R^{3d}$; $-SO_2NR^{2d}R^{3d}$; $-SO_2R^{2d}$; $-CF_3$; $-(CH_2)_{0-6}-OR^{2d}$; -OH, $-OC_{1-6}$alkyl, ,$-O-(CH_2)_{1-6}OR^{2d}$; $-O-(CH_2)_{1-6}-C(=O)-O-R^{2d}$; $-O-(CH_2)_{1-6}-C(=O)-N(R^{2d},R^{3d})$; $-N(R^{5a})-(CH_2)_{1-6}-OR^{2d}$; $-N(R^{5a})-(CH_2)_{1-6}-N(R^{2d},R^{3d})$; $-C(=O)-N(R^{2d},R^{3d})$; $-N(R^{5a})-(CH_2)_{1-6}-C(=O)-N(R^{2d},R^{3d})$; $-N(-(CH_2)_{1-6}-OR^{2d})_2$; $-N(R^{5a})-(CH_2)_{1-6}-OR^{2d}$; $-N(R^{5a})-C(=O)-R^{2d}$; $-N(R^{5a})-SO_2-R^{2d}$; $-(CH_2)_{0-6}-C(=O)-O-R^{2d}$; $-(CH_2)_{0-6}-C(=O)-N(R^{2d},R^{3d})$; $-(CH_2)_{0-6}-C(=NR^{2d})-N(R^{3d},R^{4d})$; $-(CH_2)_{0-6}-N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d})$; a $-(CH_2)_{0-6}-N(R^{3d})C_{5-6}$ membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, and a $-(CH_2)_{0-6}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{5a}, R^{2d}, R^{3d} and R^{4d} are each independently a member selected from the group consisting of:

H, C_{1-6}-alkyl and C_{1-6}-alkylaryl, -CN; $-NO_2$; carbocylic aryl, -CN; $-NO_2$; or

R^{2d} and R^{3d} taken together with the N atoms they are independently attached form a 5-7 membered saturated, partially unsaturated or aromatic heterocyclic ring; or

R^{3d} and R^{4d} taken together with the N atom to which they are attached form a 5-8 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

J is a direct link or is a member selected from the group consisting of:
$-N(-R^9)-C(=O)-$; $-C(=O)-N(-R^9)-$; $-O-$; $-S-$; $-SO-$; $-SO_2-$; $-CH_2-$; $-N(-R^9)-$; and $-N(-R^9)-SO_2-$;

R^9 is a member selected from the group consisting of:
H; $-C_{1-4}$-alkyl; $-C_{0-4}$-alkyl-carbocyclic aryl; $-(CH_2)_{0-4}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S; $-(CH_2)_{1-6}-C(=O)-O-C_{1-4}$-alkyl; and $-(CH_2)_{1-6}-C(=O)-N(R^{6a},R^{6b})$;

R^{6a} and R^{6b} are each a member independently selected from the group consisting of:
H and $-C_{1-6}$-alkyl;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0-3 R^{1e} groups;

(b) naphthyl substituted with 0-3 R^{1e} groups and

(c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and

(d) an 8-10 membered fused aromatic heterocyclic bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:

R^{3d} and R^{4d} taken together with the N atom to which they are attached form a 5-8 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

J is a direct link or is a member selected from the group consisting of:
$-N(-R^9)-C(=O)-$; $-C(=O)-N(-R^9)-$; $-O-$; $-S-$; $-SO-$; $-SO_2-$; $-CH_2-$; $-N(-R^9)-$; and $-N(-R^9)-SO_2-$;

R^9 is a member selected from the group consisting of:
H; $-C_{1-4}$-alkyl; $-C_{0-4}$-alkyl-carbocyclic aryl; $-(CH_2)_{0-4}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S; $-(CH_2)_{1-6}-C(=O)-O-C_{1-4}$-alkyl; and $-(CH_2)_{1-6}-C(=O)-N(R^{6a},R^{6b})$;

R^{6a} and R^{6b} are each a member independently selected from the group consisting of:
H and $-C_{1-6}$-alkyl;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0-3 R^{1e} groups;

(b) naphthyl substituted with 0-3 R^{1e} groups and

(c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and

(d) an 8-10 membered fused aromatic heterocyclic bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:

Halo; CF_3; -C_{1-4}-alkyl; carbocyclic aryl; -C_{0-2}-alkyl-CN; -O-R^{2e}; -C_{0-2}-alkyl-C(=O)-O-R^{2e}; -C_{0-2}- alkyl-C(=O)-N(R^{2e}, R^{3e}); -C_{0-2}-alkyl-NO_2; -C_{0-2}-alkyl-N(R^{2e}, R^{3e}); -C_{0-2}-alkyl-SO_2-N(R^{2c}, R^{3c}); -C_{0-2}-alkyl-SO_2-R^{2e}; trihaloalkyl; -O-C_{0-2}-alkyl-O-R^{2e}; -C_{0-2}-alkyl-O-R^{2e}; -O-C_{1-4}-alkyl-C(=O)-N(R^{2e}, R^{3e}); -O-C_{1-4}-alkyl-C(=O)-O-R^{2c}; -C_{0-2}-alkyl-N(R^{2c})-C(=O)-R^{3c}; -C_{0-2}-alkyl-N(-R^{2e})-SO_2-R^{3c}; -CH_2-N(R^{2e})-C(=O)-R^{3e} ;-CH_2-N(R^{2e})-SO_2-R^{3c}; -$(CH_2)_{0-6}$-$NR^{2e}R^{3e}$; -C(=O)-N(R^{2e},R^{3e}); -N(-$(CH_2)_{1-6}$-OR^{2e})$_2$; -N(R^{10})-$(CH_2)_{1-6}$-OR^{2e}; -N(R^{10})-C(=O)-R^{2e}; -N(R^{10})-SO_2-R^{2e}; -C(=N(R^{10}))-N(R^{2e},R^{3e}); and a -$(CH_2)_{0-6}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{10}, R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

H; -C_{1-4}-alkyl; -C_{0-2}-alkyl-O-R^{1g}; -C_{0-2}-alkyl-N(-R^{1g}, -R^{2g});-C_{1-4}-alkyl-carbocyclic aryl; -C_{1-4}-alkyl-heterocyclic; and R^{10} and R^{2e}, or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

R^{1g} and R^{2g} are indepedently a member selected from the group of:

H; halo; -C_{1-4}-alkyl, a carbocyclic aryl group ; a saturated, partially unsaturated or aromatic heterocyclic group; -CN; -C(=O)-N(R^{3g})R^{4g}; -C(=O)-OR^{3g}; -NO_2; -$(CH_2)_p$-$NR^{3g}R^{4g}$; -$SO_2NR^{3g}R^{4g}$; -SO_2R^{3g}; -CF_3; and -$(CH_2)_pOR^{3g}$;

p is an integer of 0-2;

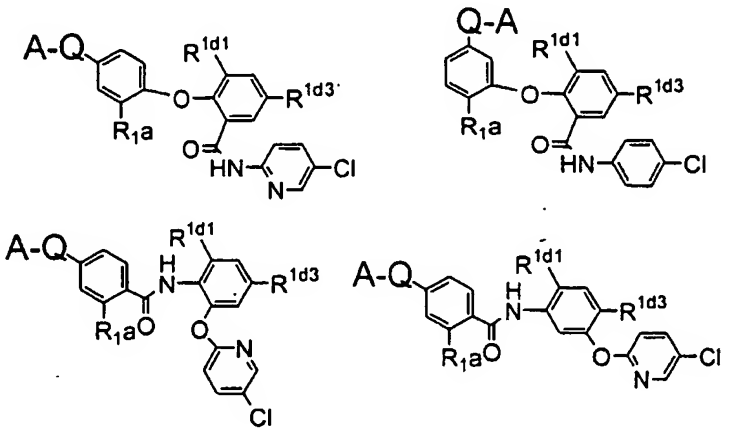
R^{3g} and R^{4g} are each independently selected from the group consisting of:

H; C_{1-4}-alkyl and -C_{0-4}-alkyl-carbocyclic aryl;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

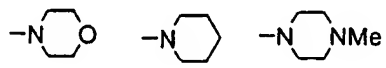
The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

R^{1a} is H or F;

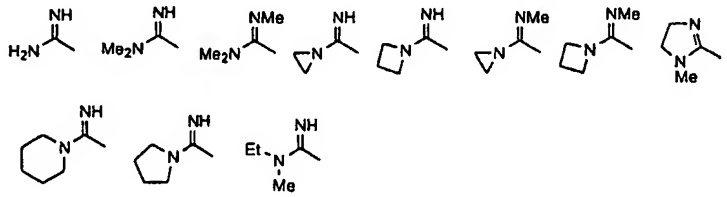
R^{1d1} is selected from H, -OMe, $-NMe_2$,



-N(Me)COOH. -N(Me)COOEt ; and

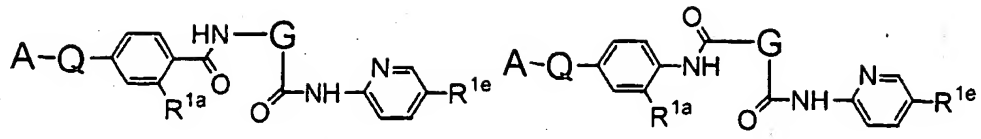
R^{1d3} is -Cl or -Br,

A-Q is a member selected from the group consisting of:



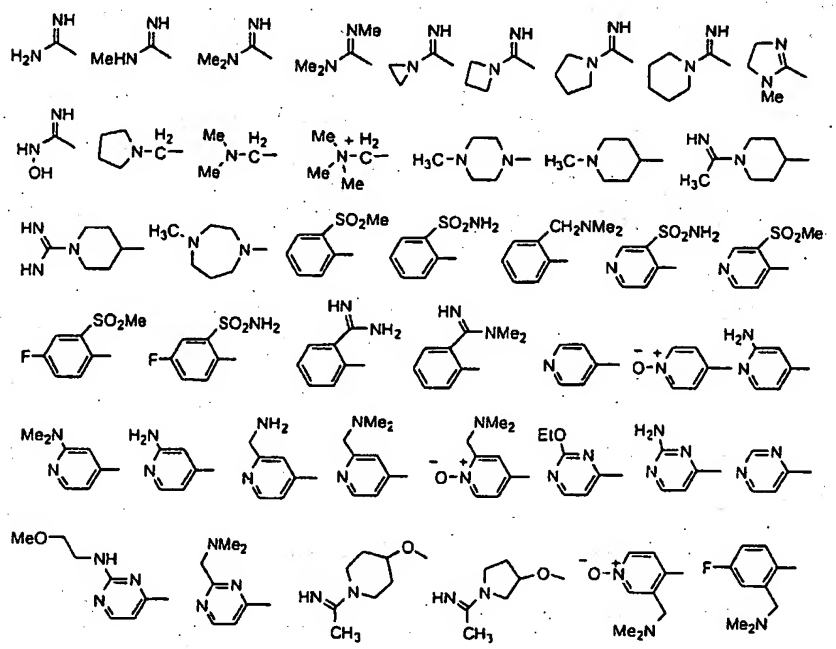
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group consisting of:



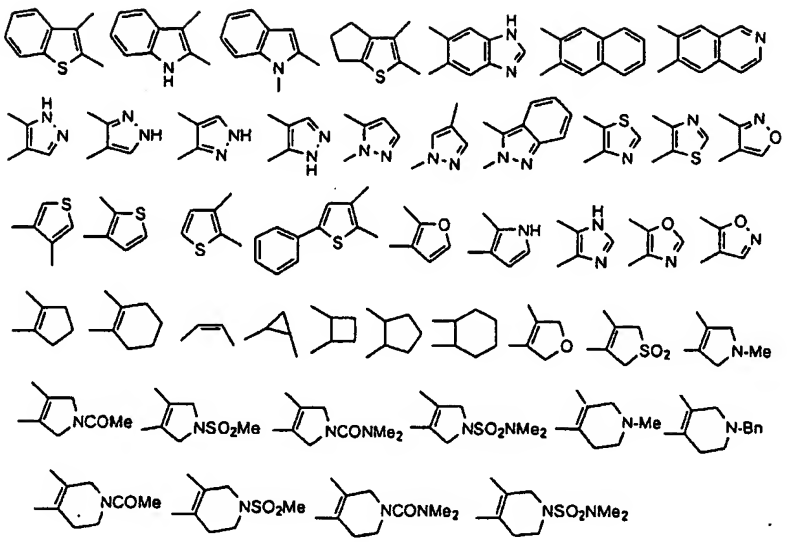
R^{1a} is a member selected from the group consisting of:

H, -F, -Cl and Br;

R^{1c} is a member selected from the group consisting of:

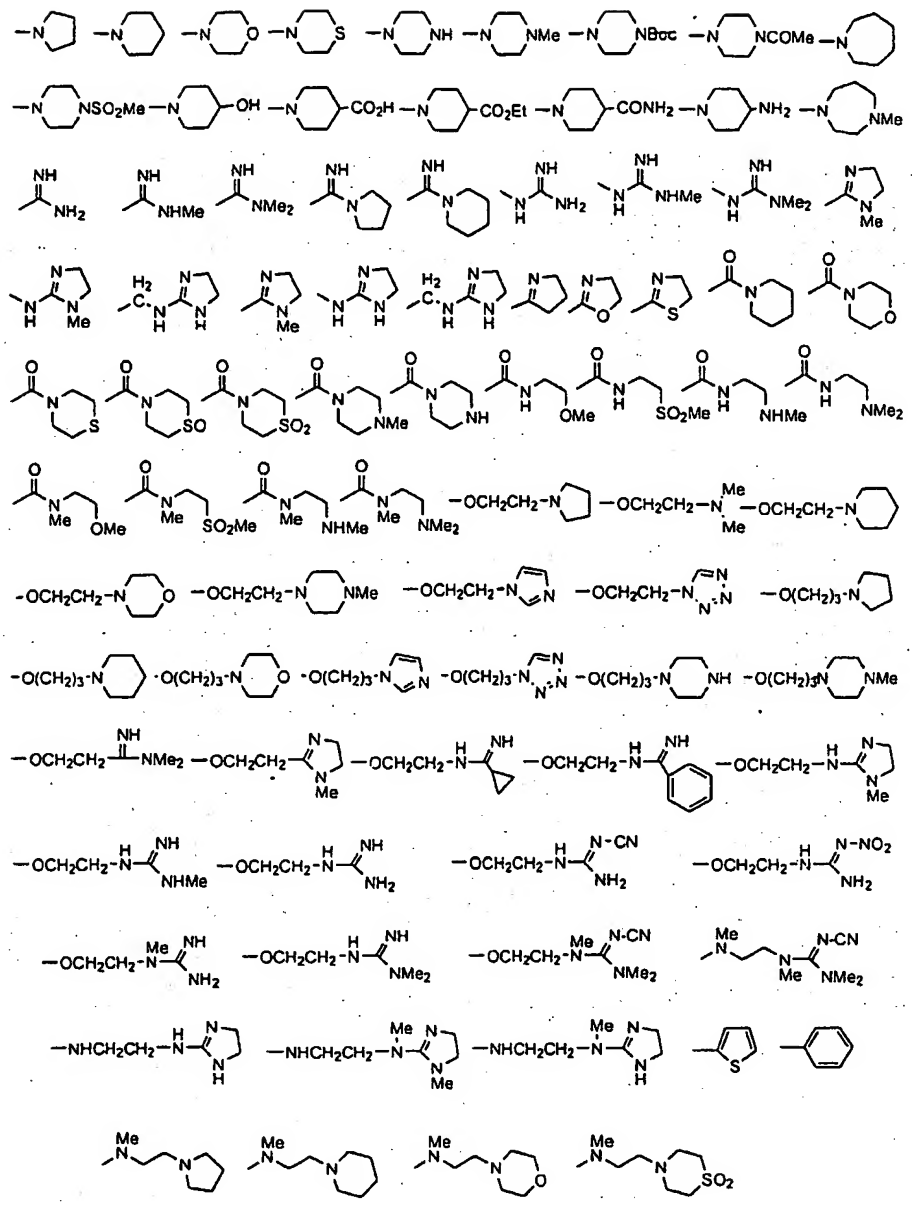
H, -F, -Cl, -Br, -OMe, -OH, -Me, $-CF_3$ and $-CH_2NH_2$; and

G is a member selected from the group consisting of:



wherein each G group is substituted by 0-4 R^{1d} groups and each such R^{1d} group is independently selected from the group consisting of:

H, -Me, -F, -Cl, -Br, aryl, heteroaryl, $-NH_2$, $-NMe_2$, -NHMe, $-NHSO_2Me$, -NHCOMe, $-CH_3$, $-CF_3$, -OH, $-OCH_3$, $-SCH_3$, $-OCF_3$, $-OCH_2F$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CF_3$, $-NO_2$, -CN, $-CO_2H$, $-CO_2Me$, $-CO_2Et$, $-CONH_2$, -CONHMe, $-CONMe_2$, $-SO_2NH_2$, $-SO_2CH_3$, $-SO_2NMe_2$, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHMe$, $-CH_2NMe_2$, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-OCH_2CO_2Et$, $-OCH_2CONH_2$, $-OCH_2CONMe_2$, $-OCH_2CONHMe$, $-OCH_2CH_2OMe$, $-OCH_2CH_2OEt$, $-OCH_2CH_2NH_2$, $-OCH_2CH_2NHMe$, $-OCH_2CH_2NMe_2$, $-NHCH_2CH_2OMe$, $-SCH_2CH_2OMe$, $-SO_2CH_2CH_2OMe$, $-OCH_2CH_2SO_2Me$, $-NHCH_2CH_2NHMe$, $-NHCH_2CH_2NMe_2$, $-N(CH_2CH_2OH)_2$, $-N(CH_2CH_2OMe)_2$, $-NHCH_2CO_2H$, $-NHCH_2CO_2Et$, $-NHCH_2CO_2Et$, $-NHCH_2CONH_2$, $-NHCH_2CONMe_2$, $-NHCH_2CONHMe$, $-N(CH_3)CH_2CO_2H$, $-N(CH_3)CH_2CO_2Et$, -(NMe)CH2COOH, -N(Me)CH2CONH2, -N(Me)CH2CH2NMe2, -N(Me)CH2CH2OMe, -NHCH2CH2OMe,



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:

embolus occurring either spontaneously or in the setting of malignancy, surgery or trauma, (d) the treatment or prevention of any coagulopathy including disseminated intravascular coagulation (including the setting of septic shock or other infection, surgery, pregnancy, trauma or malignancy and whether associated with multi-organ failure or not), thrombotic thrombocytopenic purpura, thromboangiitis obliterans, or thrombotic disease associated with heparin induced thrombocytopenia, (e) the treatment or prevention of thrombotic complications associated with extracorporeal circulation (e.g. renal dialysis, cardiopulmonary bypass or other oxygenation procedure, plasmapheresis), (f) the treatment or prevention of thrombotic complications associated with instrumentation (e.g. cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve), and (g) those involved with the fitting of prosthetic devices.

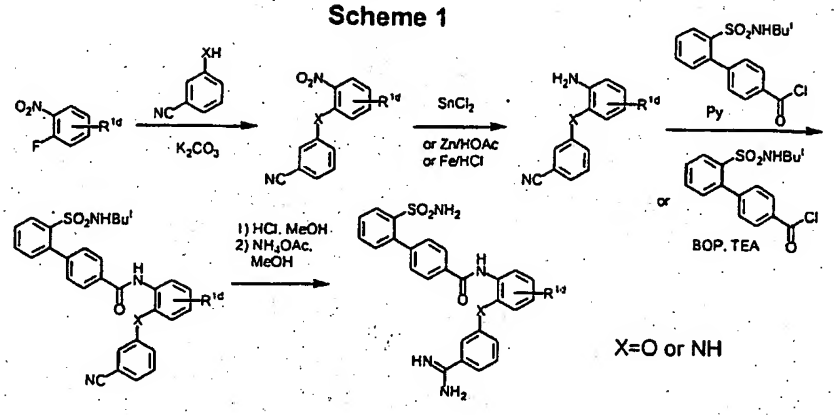
Anticoagulant therapy is also useful to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus the compounds of this invention can be added to or contacted with any medium containing or suspected to contain factor Xa and in which it is desired that blood coagulation be inhibited, e.g., when contacting the mammal's blood with material such as vascular grafts, stents, orthopedic prostheses, cardiac stents, valves and prostheses, extra corporeal circulation systems and the like.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods.

EXAMPLES

Examples of Chemical Production Process General Reaction Schemes

Scheme 1



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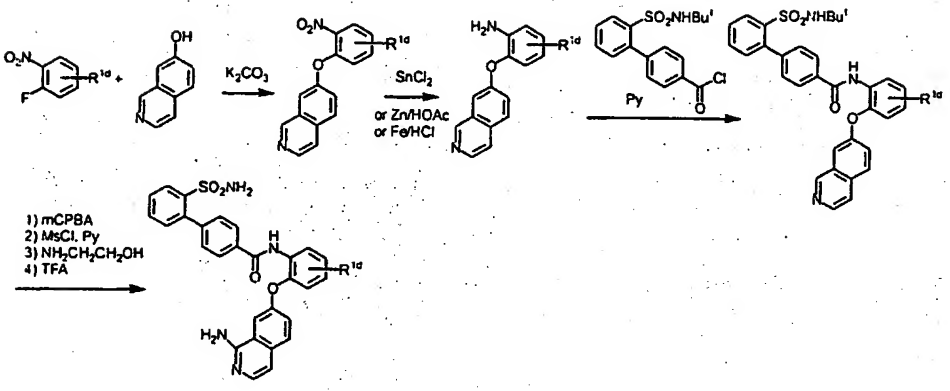
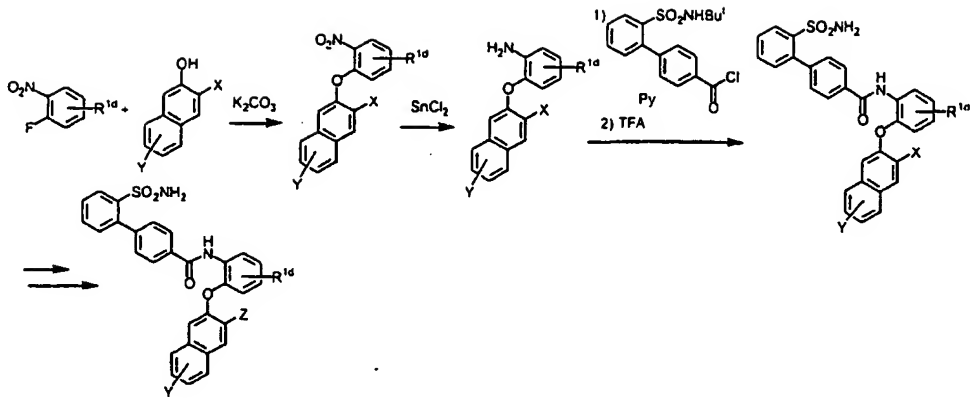
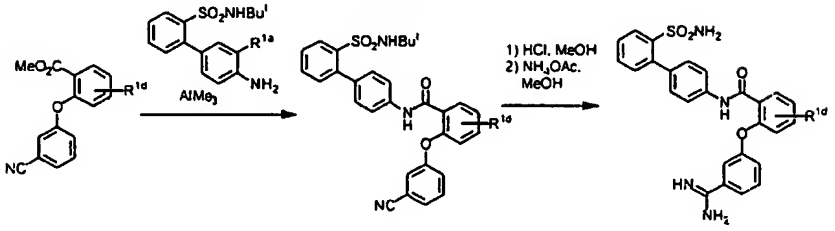
Scheme 2



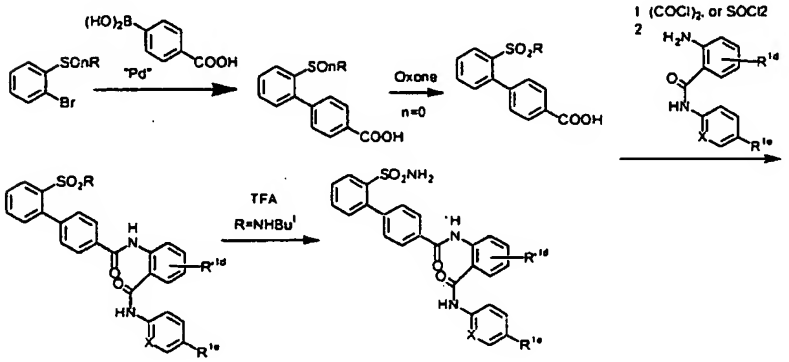
Scheme 3



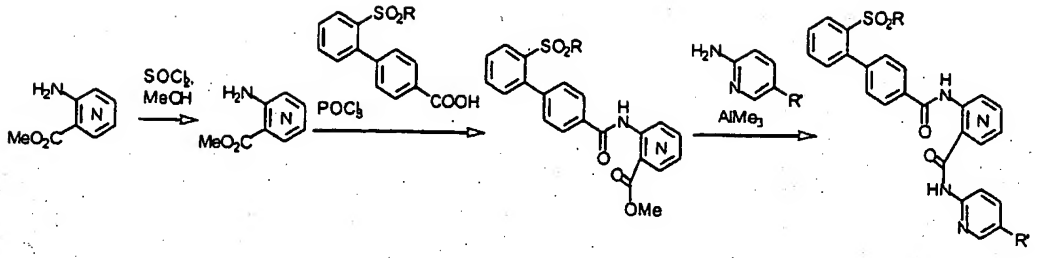
Scheme 4



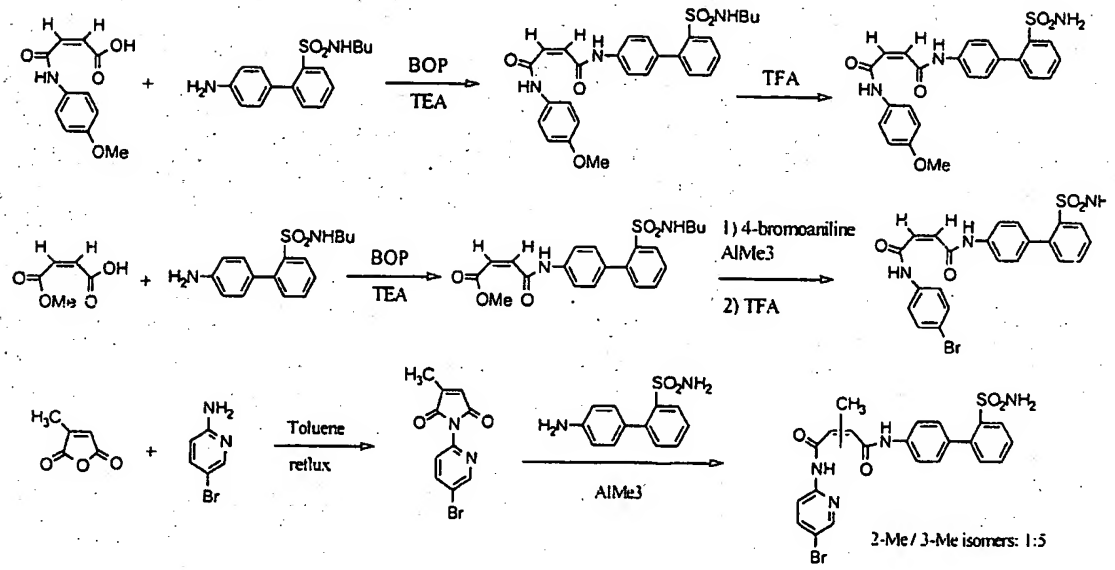
Scheme 5



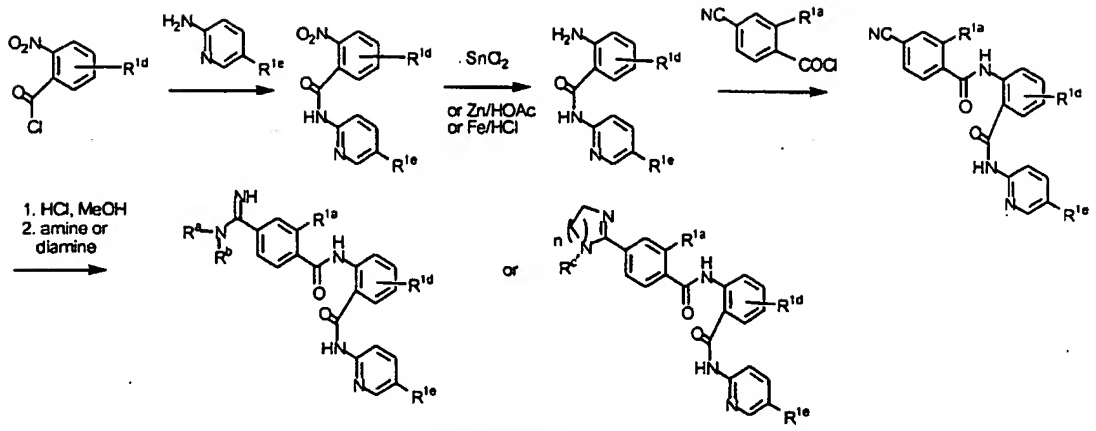
Scheme 6



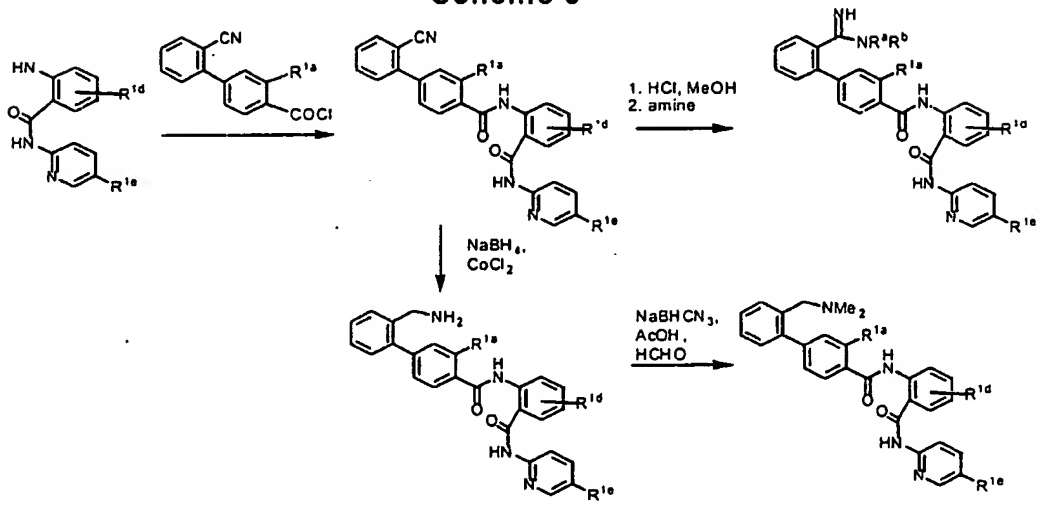
Scheme 7



Scheme 8



Scheme 9



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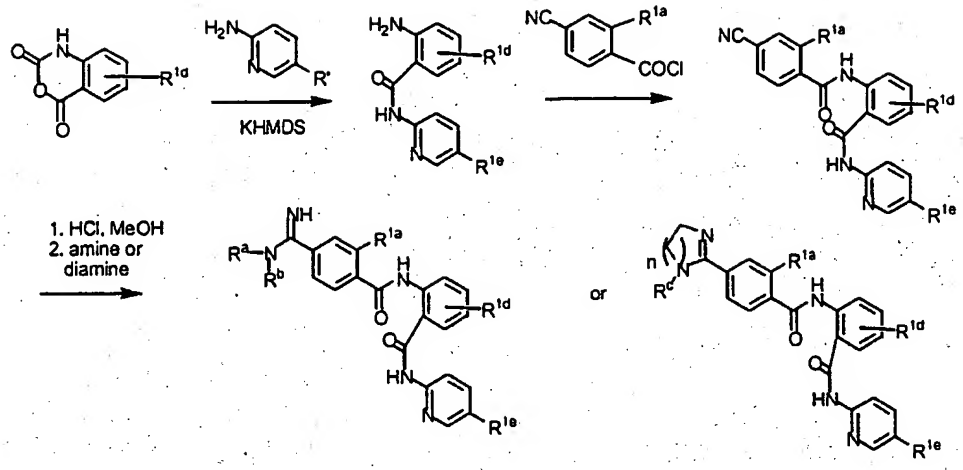
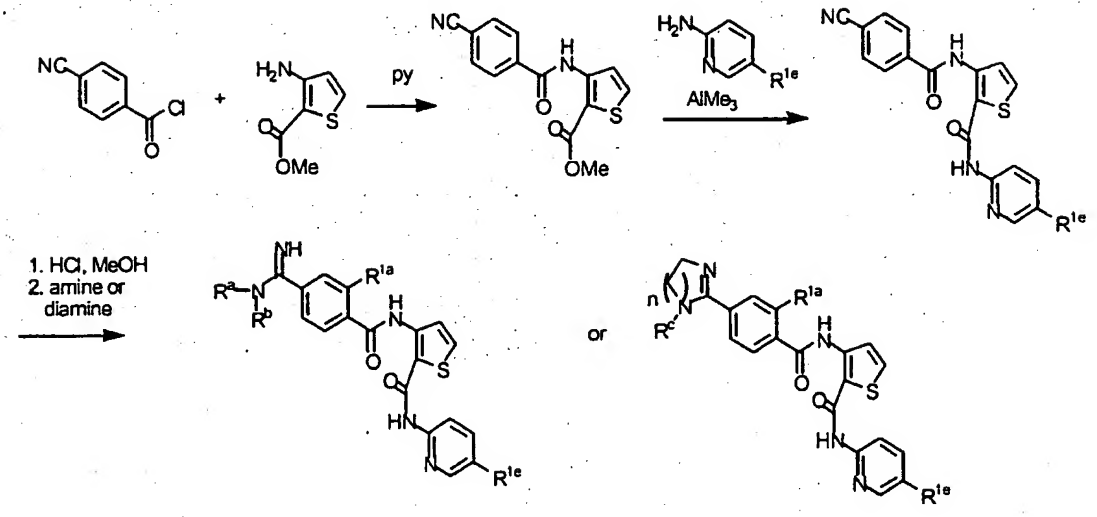
Scheme 10



Scheme 11



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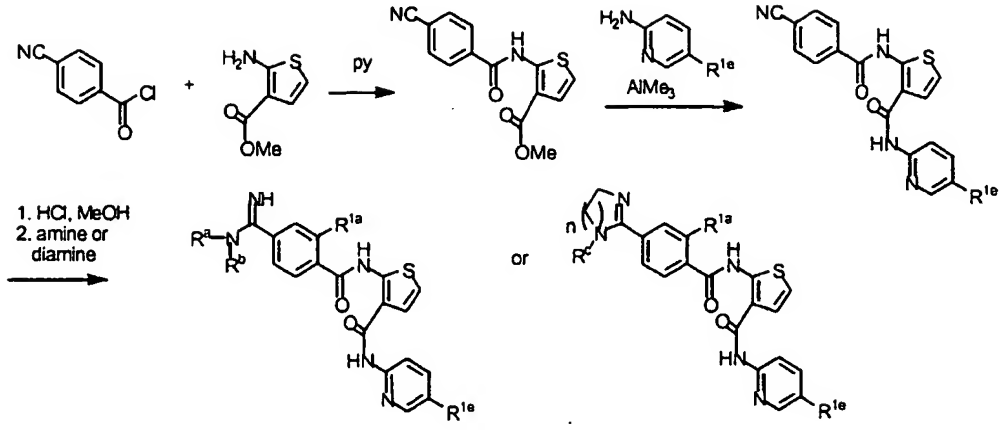
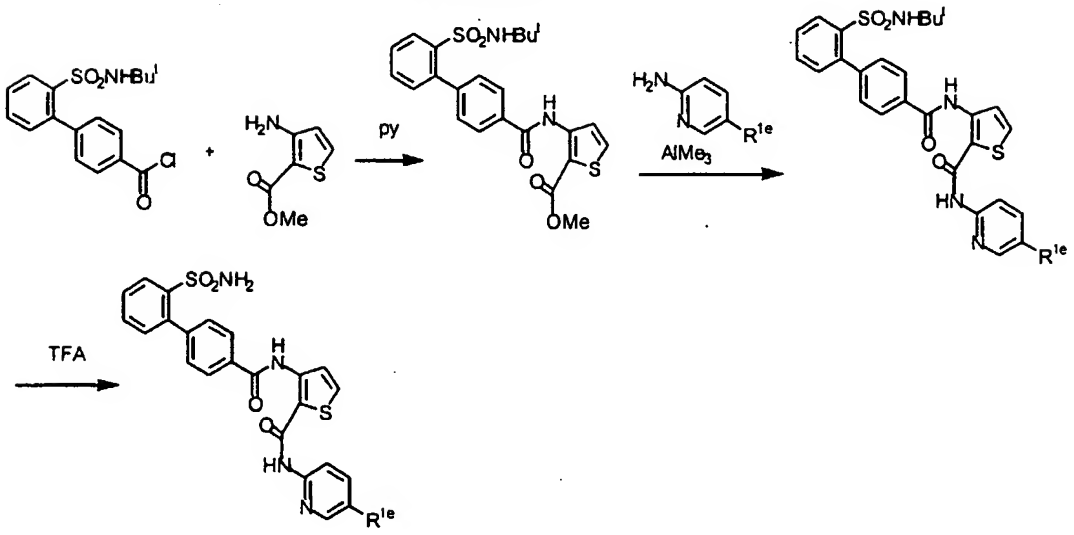
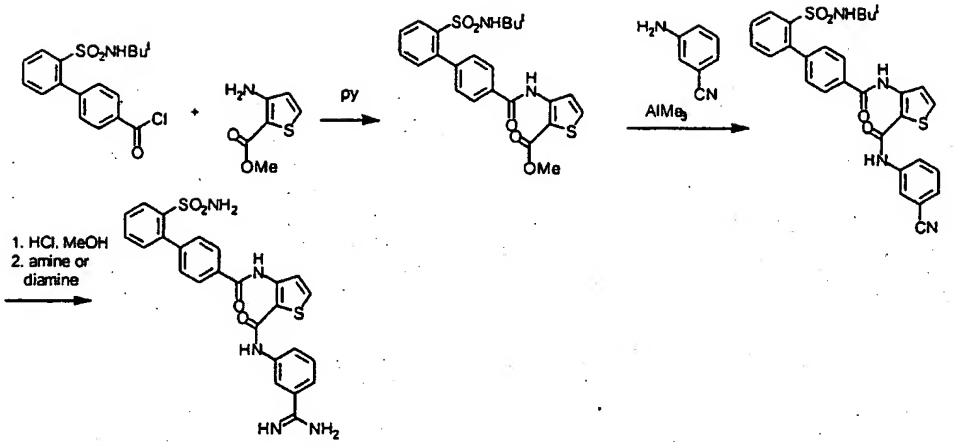
Scheme 12



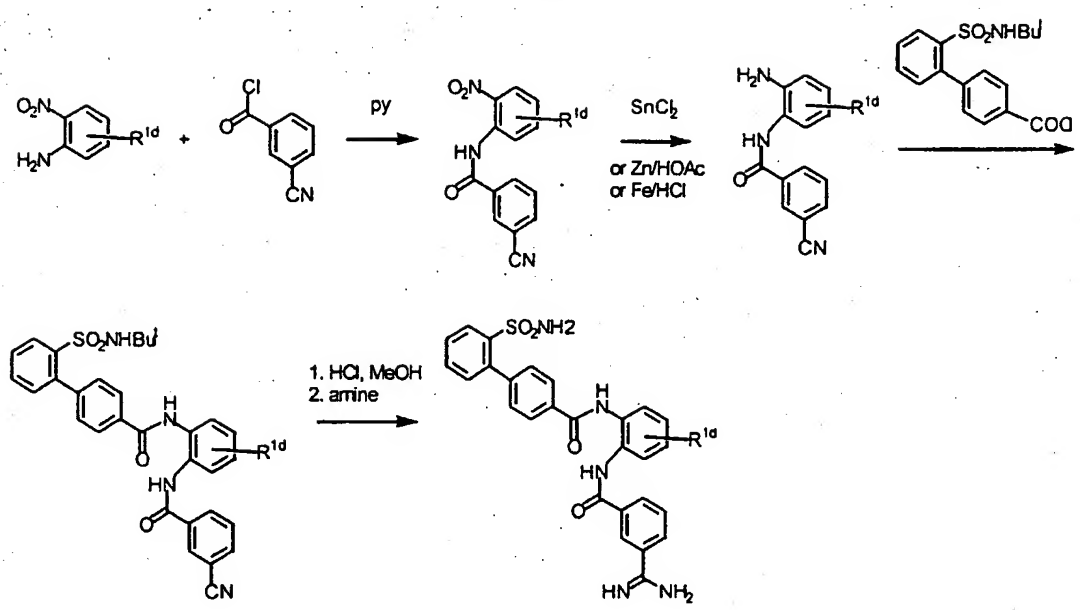
Scheme 13



Scheme 14



Scheme 15



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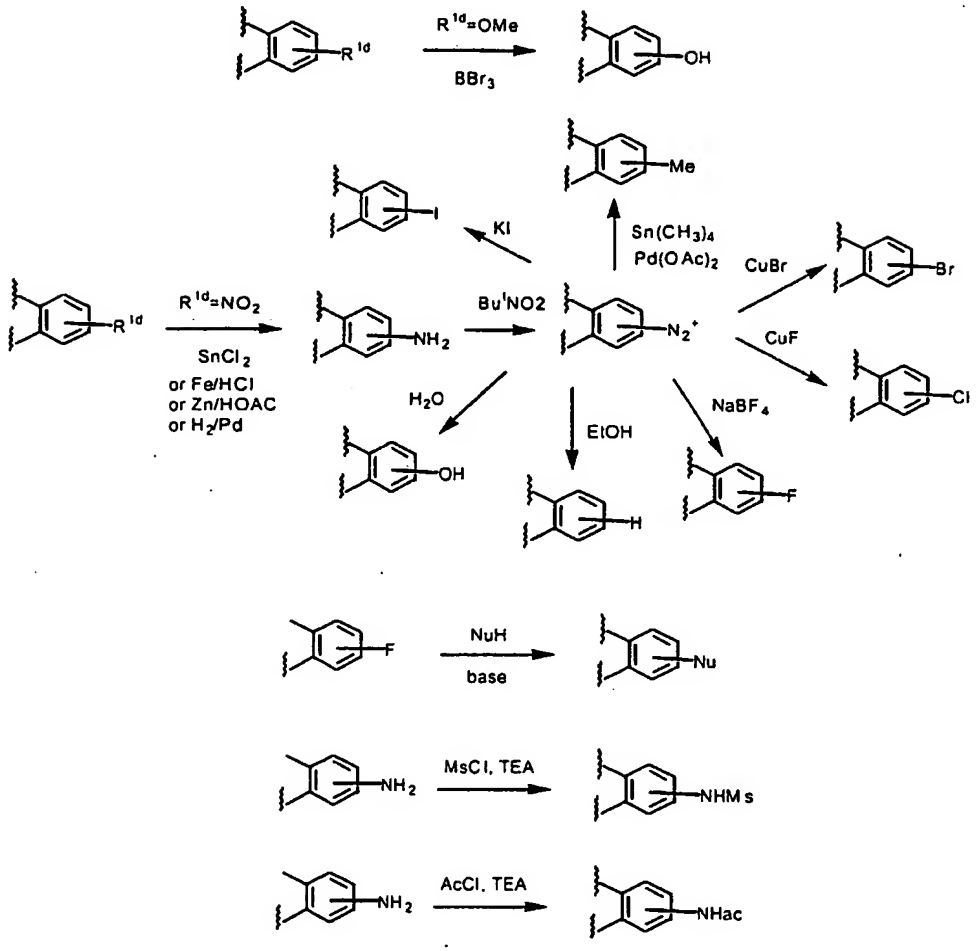
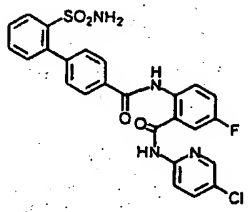
Scheme 16: Transformations of R^{1d}



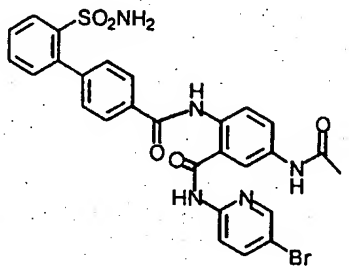
bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)-5-fluorophenylcarboxamide (120 mg, 21%). MS found for $C_{25}H_{18}BrFN_4O_4S$ $(M+H)^+$: 569, 571.

Example 129



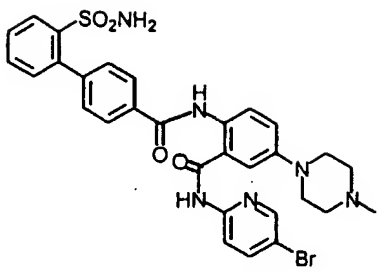
This compound was prepared according to the procedure described in example 2 with the exception of using zinc in acetic acid to reduce nitro-intermediate in step 2. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN. MS found for $C_{25}H_{18}ClFN_4O_4S$ $(M+H)^+$: 525, 527.

Example 130



This compound was prepared according to the procedure described in example 2 with the exception of using 5-acetamido-2-nitrobenzoic acid as the starting material in step 1. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN MS found for $C_{27}H_{22}BrN_5O_5S$ $(M+H)^+$: 608, 610.

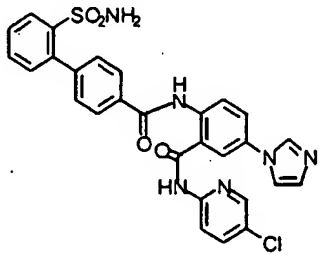
Example 131



This compound is prepared according to the procedure described in example 2 with the exception of the following step 1b performed on the nitro-intermediate from step 1. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN MS found for $C_{30}H_{29}BrN_6O_4S$ $(M+H)^+$: 649, 651.

Step 1b: A mixture of N-(5-bromo-2-pyridinyl)-(2-nitro)-5-fluorophenylcarboxamide (0.68 g, 2 mmol, 1.0 equiv), N-methylpiperazine (0.60 g, 3 equiv), and Cs_2CO_3 (1.30 g, 2 equiv) in 5 mL of dimethylformamide was stirred at 90°C overnight. Ethyl acetate was added and washed with H_2O. The organic layer was dried over Na_2SO_4, filtered, evaporated, purified via flash chromatography on silica gel to give N-(5-bromo-2-pyridinyl)-(2-nitro)-5-(4-N-methylpiperazine)phenylcarboxamide (0.54g, 65%). MS found for $C_{17}H_{18}BrN_5O_3$ $(M+H)^+$: 419, 421.

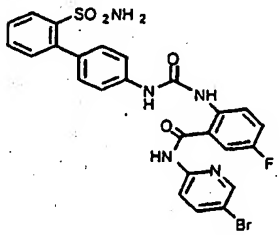
Example 132



This compound was prepared according to the procedure described in example 5. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN MS found for $C_{28}H_{21}ClN_6O_4S$ $(M+H)^+$: 573, 575.

Example 133

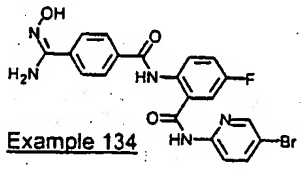
N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylaminocarbonylamino)-5-fluorophenylcarboxamide.



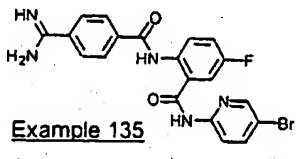
Step 3: A mixture of 4-[(2-t-butylaminosulfonyl)phenyl]phenylamine (0.180 g, 1.2 equiv), N,N'-disuccinimidyl carbonate (0.154 g, 1.2 equiv), 4-methylmorpholine (0.5 mL) in 10 mL of acetonitrile was stirred at rt for 30 min. N-(5-bromo-2-pyridinyl)-(2-amino)-5-fluorophenylcarboxamide (0.155 g, 0.5 mmol, 1.0 equiv) was added and the solution was stirred at rt for 3 hrs. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The intermediate was reacted into 5 mL of trifluoroacetic acid at rt overnight. TFA was then evaporated and the product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl] phenylaminocarbonylamino)-5-fluorophenylcarboxamide (0.053 g, 18%). MS found for $C_{25}H_{19}BrFN_5O_4S$ $(M+H)^+$: 584, 586.

Examples 134-135

N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)5-fluorophenylcarboxamide.



Example 134



Example 135

Step 1: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)5-fluorophenylcarboxamide (1.24 g, 4 mmol, 1.0 equiv), 4-cyano benzoyl chloride (0.792 g, equiv), and pyridine

substituents for each group A, Q, D, E, G, J and X which may be prepared according to the invention and be useful as factor Xa inhibitors. While, for example, compounds having the same A-Q structure but a variety of substituents or D-E-G and/or J-X structures and their substituents are described and shown, the description and illustrative examples are intended to show that compounds of the invention having a different A-Q structure can also have various combinations of D-E-G- and/or J-X structures, even though such compounds may not be illustrated in the examples. In other words, each group within the A-Q-D-E-G-J-X, as each is defined above with their substituents, may be varied and combined to form sub-genuses and compounds of the invention. The description and illustrative examples show such combinations and are not intended to limit the sub-genuses or compounds within the A-Q-D-E-G-J-X genus of the invention.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention. All the patents, journal articles and other documents discussed or cited above are herein incorporated by reference.

WHAT IS CLAIMED:

1. A compound of formula Ib:

A-Q-D-E-G-J-X (Ib)

where:

A is selected from:

(a) C_1-C_6-alkyl;

(b) C_3-C_8-cycloalkyl;

(c) -$N(R^1,R^2)$, $N(R^1,R^2)$-$C(=NR^3)$-, $N(R^1,R^2)$-$C(=NR^3)$-$N(R^4)$-, R^1-$C(=NR^3)$-, R^1-$C(=NR^3)$-$N(R^4)$-;

(d) phenyl, which is independently substituted with 0-2 R substitutuents;

(g) naphthyl, which is independently substituted with 0-2 R substitutuents;

(h) a monocyclic or fused bicyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R substitutuents;

R is selected from:

H, halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, $-CF_3$, -CN, $-(CH_2)_m-CO_2R^1$, $-(CH_2)_m-C(=O)-N(R^1, R^2)$, $-(CH_2)_m-C(=S)-N(R^1, R^2)$, $-NO_2$, $-(CH_2)_m-SO_2N(R^1, R^2)$, $-(CH_2)_m-SO_2R^1$, $-(CH_2)_mNR^1R^2$, $-(CH_2)_mOR^1$, $-(CH_2)_m-C(=NR^3)-R^1$, $-(CH_2)_m-C(=NR^3)-N(R^1,R^2)$, $-(CH_2)_m-N(R^4)-C(=NR^3)-N(R^1,R^2)$, and a 3-8 membered cyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of

halo, C_1-C_4-alkyl, -CN -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

m is an integer of 0-2;

R^1, R^2, R^3 and R^4 are independently selected from the group consisting of:
H, -$(CH_2)_{0-4}OR^5$, -$(CH_2)_{0-4}$-CO_2R^5, -$(CH_2)_{0-4}N(-R^5, -R^6)$, -$C_{1-4}$alkyl, -$C_{2-6}$alkenyl, -$C_{2-6}$alkynyl, -$C_{3-8}$cycloalkyl, -$C_{0-4}$alkyl$C_{3-8}$cycloalkyl, -$C_{0-4}$alkylaryl and -$C_{0-4}$alkylheteroaryl, and a 3-8 membered cyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2; or

R^1 and R^2, or R^2 and R^3 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, where the hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN, -CO_2R^5, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

R^5 and R^6 are independently selected from the group consisting of:
H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylaryl and -C_{0-4}alkylheteroaryl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and -NO_2; or

R^5 and R^6 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, -C_1-C_4-alkyl, -CN -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

Q is a member selected from the group consisting of:
a direct link, -CH_2-, -C(=O)-, -O-, -N(R^7)-, -N(R^7)CH_2-, - CH_2N(R^7) -, -C(=NR^7)-, -C(=O)-N(R^7)-, -N(R^7)-C(=O)-, -S-, -SO-, -SO_2-, -SO_2-N(R^7)- and –N(R^7)-SO_2-

R^7 is selected from:

H; -C_{1-4}-alkyl; -C_{0-4}-alkylaryl; -C_{0-4}-alkyl-heteroaryl; -C_{1-4}-alkyl-O-C_{1-4}-alkyl, -C_{1-4}-alkyl-N(-C_{1-4}-alkyl, -C_{1-4}-alkyl); -C_{1-4}-alkyl-C(=O)-O-C_{1-4}-alkyl, and -C_{1-4}-alkyl-C(=O)-N(-C_{1-4}-alkyl, -C_{1-4}-alkyl);

D is a direct link or is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0-2 R^{1a} substitutuents;

(b) naphthyl, which is independently substituted with 0-2 R^{1a} substitutuents; and

(c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be subsituted from 0-2 R^{1a} substitutuents;

R^{1a} is selected from:

halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, -NO_2, -$(CH_2)_n$$OR^{2a}$, -$(CH_2)_n$$NR^{2a}R^{3a}$, -$(CH_2)_n$$CO_2R^{2a}$, -$(CH_2)_n$$CONR^{2a}R^{3a}$, -$SO_2NR^{2a}R^{3a}$, -$SO_2R^{2a}$, -$CF_3$, and a 5-6 membered

aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN and -NO_2;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylaryl and -C_{0-4}alkylheteroaryl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN and -NO_2;

n is an integer of 0-2;

E is a direct link or a member selected from the group consisting of:
-C_{1-2}-alkyl-, -S-, -SO-, -SO_2-, -O-C_{0-1}-alkyl-, -C_{0-1}-alkyl-O-, -C_{0-1}-alkyl-N(-R^8)-, -N(-R^8)-C_{0-1}-alkyl-, -C_{0-1}-alkyl-C(=O)-N(-R^8)-C_{0-1}-alkyl, -C_{0-1}-alkyl-N(-R^8)-C(=O)-C_{0-1}-alkyl-, and - C_{0-1}-alkyl-N(-R^8)-C(=O)-N(-R^8)-C_{0-1}-alkyl-;

R^8 is a member selected from the group consisting of:

H; -C_{1-4}-alkyl; -C_{0-4}-alkylaryl; -C_{0-4}-alkyl-heteroaryl; -C_{1-4}-alkyl-OR^{2b}, -C_{1-4}-alkyl-N(-R^{2b}, -R^{3b}); -C_{1-4}-alkyl-C(=O)-OR^{2b}; -C_{1-4}-alkyl-C(=O)-N(-R^{2b}, -R^{3b}); -C_{0-4}-alkyl-C(=O)-R^{2b}; and –C_{0-4}-alkyl-SO_2-R^{2b};

R^{2b} and R^{3b} are each a member independently selected from the group consisting of:

H, -C_{1-4}-alkyl, -C_{1-4}-alkyl-CO_2-C_{0-4}-alkyl, -C_{0-4}-alkyl-aryl; -C_{0-4}-alkyl-heterocyclic group, and R^{2b} and R^{3b} together with the N atom to which they are attached can form a 5-8 membered heterocyclic ring containing 1-4

heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0-2 R^{1c} groups;

R^{1c} is a member selected from the group consisting of:

Halo; -C_{1-4}-alkyl; -CN, -NO_2; -C(=O)-N(-R^{2c}, -R^{3c}); -C(=O)-OR^{2c}; -$(CH_2)_q$-N(-R^{2c}, -R^{3c}); -SO_2-N(-R^{2c}, -R^{3c}); -SO_2R^{2c}; -CF_3 and -$(CH_2)_q$-OR^{2c};

R^{2c} and R^{3c} are each independently a member selected from the group consisting of:

H; -C_{1-4}-alkyl and -C_{1-4}-alkyl-aryl;

q is an integer of 0-2;

G is a member selected from the group consisting of:

(a) C_2-alkenyl or C_{3-8}-cycloalkenyl, wherein the alkenyl and cycloalkenyl attachment points are the alkenyl carbon atoms and wherein the -C_2-alkenyl or -C_{3-8}-cycloalkenyl are substituted with 0-4 R^{1d} groups;

(b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0-4 R^{1d} groups;

(d) a 3-8 membered a saturated, partially unsaturated or aromatic monocyclic ring system containing 1-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms of the heterocyclic ring may be substituted with 0-4 R^{1d} groups; and,

(d) an 8-10 membered fused cyclic system, containing 0-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms of the fused bicyclic ring system may be substituted with 0-4 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

H, halo; $-CF_3$; $-OCF_3$, $-OCF_2H$, $-OCFH_2$, $-OCH_2CF_3$, $-OCF_2CF_3$, C_{1-6}-alkyl, carbocylic aryl, -CN; $-NO_2$; $-(CH_2)_{0-6}-NR^{2d}R^{3d}$; $-(CH_2)_{0-6}-OR^{2d}$; -OH, $-OC_{1-6}$alkyl, $-O-(CH_2)_{1-6}OR^{2d}$; $-O-(CH_2)_{1-6}-NR^{2d}R^{3d}$; $-N(R^{5a})-(CH_2)_{1-6}-OR^{2d}$; $-N(R^{5a})-(CH_2)_{1-6}-N(R^{2d},R^{3d})$; $-(CH_2)_{0-6}-C(=O)-O-R^{2d}$; $-(CH_2)_{0-6}-C(=O)-N(R^{2d},R^{3d})$; $-O-(CH_2)_{1-6}-C(=O)-O-R^{2d}$; $-O-(CH_2)_{1-6}-C(=O)-N(R^{2d},R^{3d})$; $-N(R^{5a})-(CH_2)_{1-6}-C(=O)-O-R^{2d}$; $-N(R^{5a})-(CH_2)_{1-6}-C(=O)-N(R^{2d},R^{3d})$; $-N(-(CH_2)_{1-6}-OR^{2d})_2$; $-N(-(CH_2)_{1-6}-N(R^{2d},R^{3d}))_2$; $-(CH_2)_{0-6}-SO_2NR^{2d}R^{3d}$; $-(CH_2)_{0-6}-SO_2R^{2d}$; $-(CH_2)_{0-6}-N(R^{5a})-C(=O)-R^{2d}$; $-(CH_2)_{0-6}-N(R^{5a})-SO_2-R^{2d}$, $-(CH_2)_{0-6}-C(=NR^{2d})-N(R^{3d},R^{4d})$; $-(CH_2)_{0-6}-N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d})$; $-(CH_2)_{0-6}-N(R^{5a})C(=NR^{2d})-R^{4d}$; $-O-(CH_2)_{1-6}-SO_2NR^{2d}R^{3d}$; $-O-(CH_2)_{1-6}-SO_2R^{2d}$; $-O-(CH_2)_{1-6}-N(R^{5a})-C(=O)-R^{2d}$; $-O-(CH_2)_{1-6}-N(R^{5a})-SO_2-R^{2d}$, $-O-(CH_2)_{1-6}-C(=NR^{2d})-N(R^{3d},R^{4d})$; $-O-(CH_2)_{1-6}-N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d})$; $-O-(CH_2)_{1-6}-N(R^{5a})C(=NR^{2d})-R^{4d}$; $-N(R^{5d})-(CH_2)_{1-6}-SO_2NR^{2d}R^{3d}$; $-N(R^{5d})-(CH_2)_{1-6}-SO_2R^{2d}$; $-N(R^{5d})-(CH_2)_{1-6}-N(R^{5a})-C(=O)-R^{2d}$; $-N(R^{5d})-(CH_2)_{1-6}-N(R^{5a})-SO_2-R^{2d}$, $-N(R^{5d})-(CH_2)_{1-6}-C(=NR^{2d})-N(R^{3d},R^{4d})$; $-N(R^{5d})-(CH_2)_{1-6}-N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d})$; $-N(R^{5d})-(CH_2)_{1-6}-N(R^{5a})C(=NR^{2d})-R^{4d}$; and a 3-8 membered cyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl and $-NO_2$;

R^{5a}, R^{2d}, R^{3d}, R^{4d} and R^{5d} are each independently a member selected from the group consisting of:

H, C_{1-6}-alkyl and C_{1-6}-alkylaryl, -CN; $-NO_2$; or

R^{2d} and R^{3d}, or R^{3d} and R^{4d} taken together with the N atoms they are independently attached form a 3-8 membered saturated, partially unsaturated or aromatic heterocyclic ring;

J is a direct link or is a member selected from the group consisting of:

$-N(-R^9)-C(=O)-$; $-C(=O)-N(-R^9)-$; -O-; -S-; -SO-; $-SO_2-$; -SO2N(R9)-, $-CH_2-$; $-N(-R^9)-$; and $-N(-R^9)-SO_2-$;

R^9 is a member selected from the group consisting of:

H; $-C_{1-4}$-alkyl; $-C_{0-4}$-alkylaryl; $-C_{0-4}$-alkyl-heteroaryl; $-C_{1-4}$-alkyl-OR^{6a}, $-C_{1-4}$-alkyl-$N(-R^{6a}$, $-R^{6b})$; $-C_{1-4}$-alkyl-$C(=O)-OR^{6a}$, and $-C_{1-4}$-alkyl-$C(=O)-N(-R^{6a}$, $-R^{6b})$;

R^{6a} and R^{6b} are each a member independently selected from the group consisting of:

H and $-C_{1-6}$-alkyl;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0-3 R^{1e} groups;

(b) naphthyl substituted with 0-3 R^{1e} groups and

(c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and

(d) an 8-10 membered fused bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:

Halo; CF_3; $-C_{1-4}$-alkyl; carbocyclic aryl; $-C_{0-2}$-alkyl-CN; $-O-R^{2e}$; $-C_{0-2}$-alkyl-$C(=O)-O-R^{2e}$; $-C_{0-2}$- alkyl-$C(=O)-N(R^{2e}, R^{3e})$; $-C_{0-2}$-alkyl-NO_2; $-C_{0-2}$-alkyl-$N(R^{2e}, R^{3e})$; $-C_{0-2}$-alkyl-$SO_2-N(R^{2e}, R^{3e})$; $-C_{0-2}$-alkyl-SO_2-R^{2e}; trihaloalkyl; $-O-C_{0-2}$-alkyl-$O-R^{2e}$; $-C_{0-2}$-alkyl-$O-R^{2e}$; $-O-C_{1-4}$-alkyl-$C(=O)-N(R^{2e}, R^{3e})$; $-O-C_{1-4}$-alkyl-$C(=O)-O-R^{2e}$; $-C_{0-2}$-alkyl-$N(R^{2e})-C(=O)-R^{3e}$; $-C_{0-2}$-alkyl-$N(-R^{2e})-SO_2-R^{3e}$; $-CH_2-N(R^{2e})-C(=O)-R^{3e}$;$-CH_2-N(R^{2e})-SO_2-R^{3e}$;

$-(CH_2)_{0-6}-NR^{2e}R^{3e}$; $-C(=O)-N(R^{2e},R^{3e})$; $-N(-(CH_2)_{1-6}-OR^{2e})_2$; $-N(R^{10})-(CH_2)_{1-6}-OR^{2e}$; $-N(R^{10})-C(=O)-R^{2e}$; $-N(R^{10})-SO_2-R^{2e}$; $-C(=N(R^{10}))-N(R^{2e},R^{3e})$; and a $-(CH_2)_{0-6}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{10}, R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

H; $-C_{1-4}$-alkyl; $-C_{0-2}$-alkyl-O-R^{1g}; $-C_{0-2}$-alkyl-N(-R^{1g}, -R^{2g});-C_{1-4}-alkyl-carbocyclic aryl; $-C_{1-4}$-alkyl-heterocyclic; and R^{10} and R^{2e}, or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

R^{1g} and R^{2g} are indepedently a member selected from the group of:

H; halo; $-C_{1-4}$-alkyl, a carbocyclic aryl group ; a saturated, partially unsaturated or aromatic heterocyclic group; -CN; $-C(=O)-N(R^{3g})R^{4g}$; $-C(=O)-OR^{3g}$; $-NO_2$; $-(CH_2)_p-NR^{3g}R^{4g}$; $-SO_2NR^{3g}R^{4g}$; $-SO_2R^{3g}$; $-CF_3$; and $-(CH_2)_pOR^{3g}$;

p is an integer of 0-2;

R^{3g} and R^{4g} are each independently selected from the group consisting of:

H; C_{1-4}-alkyl and $-C_{0-4}$-alkyl-carbocyclic aryl;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

2. A pharmaceutical composition for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 1.

3. A method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising administering to said mammal a therapeutically effective amount of a compound of claim 1.

4. The method of claim 4, wherein the condition is selected from the group consisting of:

acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation, and thrombotic complications associated with the fitting of prosthetic devices.

5. A method for inhibiting the coagulation of a biological sample comprising the step of administering a compound of claim 1.

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(54) Title: BENZAMIDES AND RELATED INHIBITORS OF FACTOR XA

(57) Abstract: Benzamide compounds of formula A-Q-D-E-G-J-X, where the variables are as defined in the claims, including their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives having activity against mammalian factor Xa are described. Compositions containing such compounds are also described. The compounds and compositions are useful in vitro or in vivo for preventing or treating coagulation disorders.

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/75 C07C317/44 C07D213/80 C07D213/79 C07C311/46
C07D401/12 C07D233/26 C07D295/18 C07C257/18 C07D203/18
C07D205/04 C07D409/14 C07D409/12 C07D401/14 C07D231/40
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 937 711 A (ROCHE DIAGNOSTICS) 25 August 1999 (1999-08-25) the whole document ---	1-5
X	WO 99 00127 A (ELI LILLY) 7 January 1999 (1999-01-07) the whole document ---	1-5
X	"Dictionary of Organic Compounds, 5th Ed., Vol. 5" 1982 , CHAPMAN AND HALL , NEW YORK, NY, US XP002161122 157909 compounds T-00160, T-00161, T-00162 page 5119 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 January 2002	25/01/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	English, R

2

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INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/US 01/06247

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/12 C07D217/22 C07D333/38 A61K31/18 A61K31/44 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

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Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	H.J. SPIE, ET AL.: "An improved synthesis of aryl sulphones" SYNTHESIS, no. 3, March 1984 (1984-03), pages 283-284, XP002161121 Georg Thieme Verlag, Stuttgart, DE ISSN: 0039-7881 compound 3c --- -/--	1

[X] Further documents are listed in the continuation of box C.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 January 2002	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	English, R

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	T. KEUMI, ET AL.: "2-(Trifluoromethylsulphonyloxy)pyridine as a reagent for the ketone synthesis from carboxylic acids and aromatic hydrocarbons" BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, vol. 61, no. 2, February 1988 (1988-02), pages 455-460, XP002161120 Japan Publications Trading Co., Tokyo, JP ISSN: 0009-2673 table 1, entry 13, product ---	1
X	H. SUZUKI, ET AL.: "Selective reduction with lithium aluminium hydride / diphosphorus tetraiodide" CHEMISTRY LETTERS, no. 6. June 1983 (1983-06), pages 909-910, XP002161110 Chemical Society of Japan, Tokyo, JP ISSN: 0366-7022 table 1. entry 5 ---	1
X	J.D. YOUNG. ET AL.: "Interannular interactions in para-substituted diphenylmethane anion radicals" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 94. no. 25, 13 December 1972 (1972-12-13), pages 8790-8794. XP002161109 American Chemical Society, Washington, DC, US ISSN: 0002-7863 compound 3b ---	1
X	W.F. COCKBURN, ET AL.: "Molecular rearrangement of tertiary amines. Part I" JOURNAL OF THE CHEMICAL SOCIETY, no. 8, August 1960 (1960-08), pages 3340-3346, XP002161112 Royal Society of Chemistry, Letchworth, GB page 3343, line 4 - line 5 ---	1
X	R. KAHN, ET AL.: "Addition von Maleinsäure-anhydrid an Polyene. (Über konjugierte Doppelbindungen, XIV)" BERICHTE DER DEUTSCHEN CHEMISCHEN GESELLSCHAFT, vol. 63, 1930, pages 2662-2679, XP002161030 Verlag Chemie, Weinheim, DE compound IV ---	1

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2